

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 7/42, 7/48	A1	(11) International Publication Number: WO 94/07460 (43) International Publication Date: 14 April 1994 (14.04.94)
(21) International Application Number: PCT/US92/08215 (22) International Filing Date: 2 October 1992 (02.10.92) (30) Priority data: 954,177 30 September 1992 (30.09.92) US (71) Applicant: HENKEL CORPORATION [US/US]; 140 Germantown Pike, Suite 150, Plymouth Meeting, PA 19462 (US). (72) Inventors: SALKA, Barry, A. ; 39-02 Knott Terrace, Fair Lawn, NJ 07410 (US). BARABASH, Martin, J. ; One Sawgrass Court, Jamesburg, NJ 08831 (US). JABLONSKI, Robert, M. ; 74 71st Street, Brooklyn, NY 11209 (US). VALDES, Arturo ; 720 Boulevard East, Weehawken, NJ 07087 (US).		(74) Agent: JAESCHKE, Wayne, C.; Henkel Corporation, 140 Germantown Pike, Suite 150, Plymouth Meeting, PA 19462 (US). (81) Designated State: CA. Published <i>With international search report.</i>
(54) Title: METHODS FOR IMPROVING UV ABSORBANCE OF SUNSCREEN COMPOUNDS (57) Abstract Methods for increasing the UV absorbance of certain sunscreen agents for topical applications yielding compositions exhibiting improved sun protection factor (SPF) are disclosed. These methods comprise dissolving or suspending octyl methoxycinnamate or benzophenone-3 in certain emollient systems, e.g. high polar type materials such as ethoxylates resulting in a 15% increase in UV absorbance.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BG	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CF	Central African Republic	KR	Republic of Korea	SD	Sudan
CG	Congo	KZ	Kazakhstan	SE	Sweden
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovak Republic
CM	Cameroon	LU	Luxembourg	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	MC	Monaco	TG	Togo
CZ	Czech Republic	MG	Madagascar	UA	Ukraine
DE	Germany	ML	Mali	US	United States of America
DK	Denmark	MN	Mongolia	UZ	Uzbekistan
ES	Spain			VN	Viet Nam
FI	Finland				

S P E C I F I C A T I O N

METHODS FOR IMPROVING UV ABSORBANCE OF SUNSCREEN COMPOUNDS

of which the following is a specification:

1. Field of the Invention

5 The present invention relates to methods for increasing the UV absorbance of certain sunscreen agents for topical applications yielding compositions exhibiting improved sun protection factor (SPF). These methods comprise dissolving or suspending octyl methoxycinnamate or benzophenone-3 in certain emollient systems resulting in a 15% increase in UV absorbance.

2. Background of the Invention

10 The sun emits energy in a continuous band throughout the electromagnetic spectrum which includes the ultraviolet range (200-400 nm), that part of the spectrum that tans and burns the skin. Prolonged exposure of a person's skin to

the sunlight may cause a variety of conditions. For example, it can cause premature aging of the skin. In some cases, it may cause the development of skin cancers such as basal cell cancer, squamous cell cancer and melanoma. See
5 for example, Blum, H.P. "Sunlight As An Environmental Factor in Cancer of the Skin". Military Medicine, 117: 202, 1955; Consequently, many products or measures have been marketed to protect the skin from the harmful effects of excessive exposure to the sun. Sunscreen agents such as
10 octyl methoxycinnamate and benzophenone-3 have gained wide acceptance. These agents act by absorbing UV light thereby offering the selective protection against the harmful effects of UV wave bands. In use, the compounds are dissolved or suspended in solvent systems such as ethanol,
15 isopropanol, propylene glycol, and mineral oil, and the resulting compositions applied to the skin.

3. Description of the Related Art

"Encyclopedia of UV Absorbers for Sunscreen Products" in Cosmetics and Toiletries, vol. 201, March 1987 authored
20 by Dr. N. Shaath and published by Allured Publishing Corp. describes benzophenone-3 as well as octyl methoxycinnamate as sunscreen agents. Under the monograph of each of these compounds, there are among others a description of their UV properties. These monographs are incorporated herein by
25 reference. The UV properties are determined by measuring the wavelength of maximum absorption (λ_{\max}) in the appropriate solvents [ethyl alcohol (EA) or mineral oil (MO)]. It is recorded, along with the molar extinction coefficient or molar absorptivity (ϵ) and the K Value.

30 For benzophenone-3, the UV properties are:

λ_{\max} (EA): 288/325 λ_{\max} (MO): 288/329 nm

ϵ : 14,000/9,400 (c: 4.67 mg/L in EA)
17,700/7,800 (c: 4.00 mg/L in MO)

K Value (EA): 41

and for octyl methoxycinnamate the UV properties are:

$$\lambda_{\max}(\text{EA}): 311 \text{ nm} \quad \lambda_{\max}(\text{MO}): 289 \text{ nm}$$

$$\epsilon: \begin{array}{l} 23,300 \text{ (c: 8.27 mg/L in EA)} \\ 19,700 \text{ (c: 10.24 mg/L in MO)} \end{array}$$

5

K Value (EA): 84

There are several patents disclosing the use of various sunscreen agents. For example, U.S. patent 4,940,577 issued July 10, 1990 discloses a water-in-oil emulsion containing as a sunscreen agent compounds such as octyl dimethyl PABA, octyl methoxycinnamate, benzophenone-3, octyl salicylate and mixtures thereof. Other patents, e.g. U.S. patents 4,940,574, 4,919,934, 4,894,222, 4,869,897, 4,851,434 and 4,847,072 disclose the use of benzophenone-3 and others as sunscreen agents.

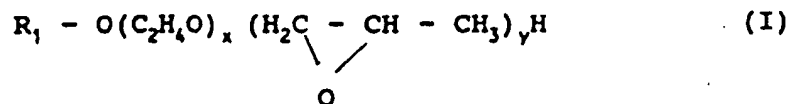
U.S. patents 5,075,333 and 5,061,733 discloses the use of Cetiol LC (caprylic/capric acid/coco ester) and Cetiol V (decyl oleate) in creams and gels.

4. Summary of the Invention

In accordance with this invention, we provide a method whereby there is a significant increase in absorbance for octyl methoxycinnamate and benzophenone-3 with no significant shift in wavelength of maximum absorbance. In general, we provide a method whereby there is a minimum of 15% increase in absorbance of these compounds.

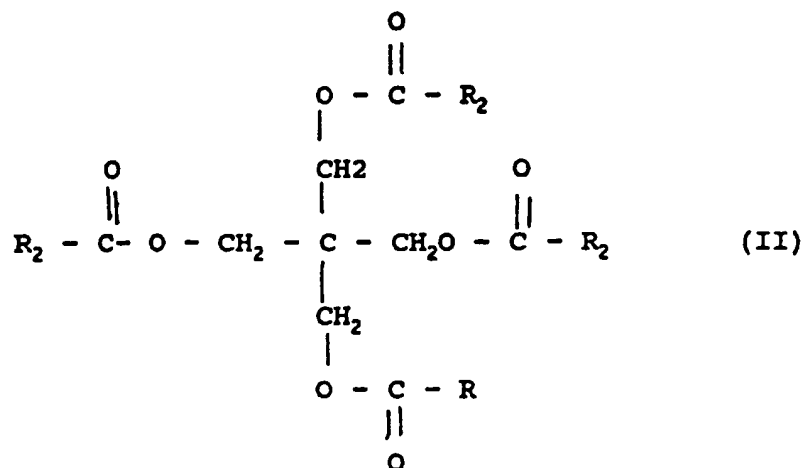
Broadly speaking, we have found that the UV absorbance of octyl methoxycinnamate is significantly increased when it is dissolved or suspended in certain highly polar type materials, i.e. ethoxylates and more particularly the following compounds: I, II, III, IV, V and VI.

4



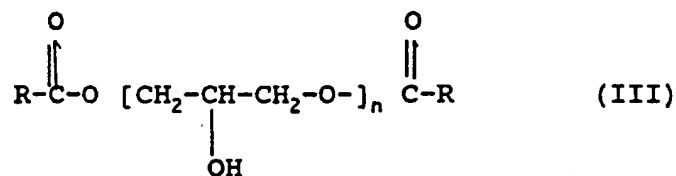
wherein R₁ is C₁₀-C₁₈ straight or branched chain alkyl, x is an integer of 5 to 10 and y is an integer of 2 to 6.

5



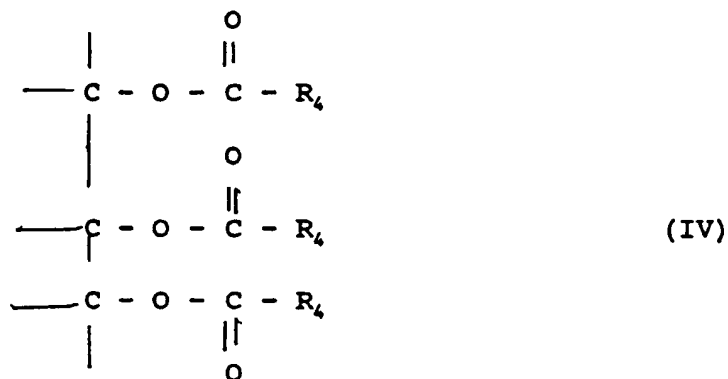
10

wherein RCO is a pelargonic acid radical



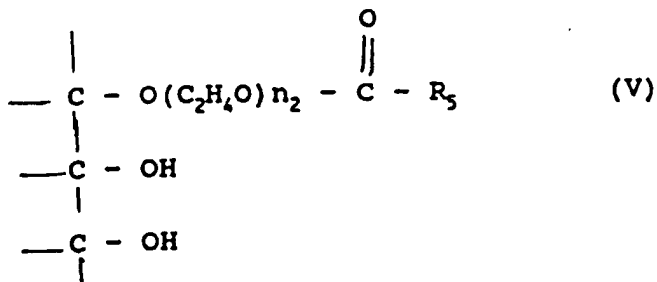
15

wherein R is an isostearic acid radical and n is an integer of 2 to 5.



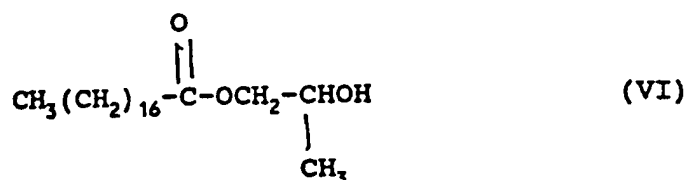
20

wherein R_4 is C_8 to C_{12} alkyl, and



5

wherein $R_5\text{CO}=\text{COCO}$ and n_2 is an integer of 4 to 9, and



10 For benzophenone-3, the UV absorbance is significantly increased when it is dissolved or suspended in solvents III, IV and VI or mixtures thereof.

15 In an abbreviated SPF test, we have found that the novel system described herein exhibits significant increases in SPF when compared to the system using mineral oil.

SPF as used herein means the test used by the FDA which is essentially the ratio of the amount of energy required to produce a minimum erythematous dose (MED) to the amount of energy to produce the same MED without any treatment by the product.

20

5. Detailed Description of the Invention

The present invention is directed to a method and means whereby there is an increase in UV light absorbance with no significant shift in wavelength of maximum absorbance for the known sunscreen agents, octyl methoxycinnamate and benzophenone-3. The present invention also includes within its scope compositions comprising

25

these compounds exhibiting not only enhanced UV absorbance but also have emollient properties for topical application.

The method of the present invention comprises mixing together an effective sunscreen amount of octyl methoxycinnamate and benzophenone-3 in the selected system, i.e. the compounds identified as I to VI above either alone or as a blend as a binary or tertiary system. The results are tabulated in Tables I and II.

TABLE I
OCTYL METHOXYCINNAMATE

<u>Solvent</u> <u>Change</u>	<u>Wavelength M.A.</u>	<u>Absorbance</u>	<u>Δ</u>
IPA	309.0	0.345	-
Mineral Oil	291.5	0.360	+ 4.3
PEG-7 Glyceryl Cocoate	310.0	0.458	+32.8
Caprylic/Capric Triglyceride	308.0	0.405	+17.4
PPG-2-Ceteareth-9 Caprate	310.0	0.444	+28.6
Isopropyl Myristate	307.0	0.371	+ 7.5
Octyl Stearate	307.0	0.310	-10.1
Hexyl Laurate	307.0	0.353	+ 2.3

TABLE II
BENZOPHENONE-3

	<u>Solvent</u> <u>Change</u>	<u>Wavelength</u> <u>nm</u>	<u>Absorbance</u> <u>2</u>	<u>Δ</u>
5	IPA	323.0	0.204	-
	Mineral Oil	327.0	0.172	-15.7
10	PEG-7 Glyceryl Cocoate	323.5	0.243	+19.1
	Caprylic/Capric Triglyceride	328.0	0.205	+ 0.5
15	PPG-2-Ceteareth-9 Caprate	323.0	0.241	+18.1
	Coco Caprylate/ Caprate	326.5	0.179	-12.3
20	Octyl Stearate	328.5	0.191	- 6.4
	Hexyl Laurate	327.0	0.197	- 3.4
25				

30 The above results are obtained by combining the selected sunscreen agent at about 500 ppm in the system as described. The above results also demonstrate the surprising effect of the present invention as not all polar compounds have the positive influence in increasing UV absorbance.

35 Examples of commercially available solvents which fall within I are PPG-5-laureth-5 and PPG-2-ceteareth-9; those which fall within II include pentaerythrityl tetrapelargonate; those which fall within III include polyglycerol-3 diisostearate; those which fall within IV include caprylic/capric triglyceride and those which fall within V include PEG-7-glyceryl cocoate and those which fall within VI include propylene glycol isostearate.

For octyl methoxycinnamate the combination of PEG-7-glyceryl cocoate with pentaerytritol tetrapelargonate at an approximate ratio of about 75:25, a combination of PPG-2-ceteareth-9 : caprylic/capric triglyceride at an approximate 50:50 and a combination of polysorbate 20 : PPG-2-ceteareth-9 : caprylic/capric triglyceride at an approximate ratio of about 50:25:25 and glycerol cocoate: propylene glycol isostearate at an approximate ratio of 50:50 is advantageous as the resulting composition exhibits a 20% increase in UV absorbance. For benzophenone-3, a combination of PEG-7-glyceryl cocoate : polyglycerol-3 diisostearate at an approximate ratio of 75:25 and a combination of polysorbate 80 : PPG-5-laureth-5 : caprylic/capric triglyceride at an approximate ratio of 50:25:25 is advantageous as these exhibit a 20% increase in UV absorbance.

As those skilled in the art would appreciate for topical applications, sunscreen composition must be non-toxic and non-irritating to the skin and capable of application to the skin as a uniform continuous film, i.e. an emollient effect. In addition, the active sunscreen affects must remain chemically stable in the vehicle for topical application. The compositions of sunscreen agents prepared in accordance with the present exhibit these desirable properties in addition to enhanced UV absorbance. In an abbreviated SPF test involving five people per sunscreen agents, there was a significant increase in SPF when compared to the same agent dissolved in mineral oil.

In a commercial embodiment of the present invention, the system may include other agents traditionally used in formulating sunscreen products. These agents include for example preservatives (such as methyl and propyl paraben) fragrance, anti-oxidants, wetting agents, emulsifiers, emulsion stabilizers and the like.

In order to further illustrate the practice of the invention, the following examples are included:

Exempl 1

Emulsions were prepared as follows:

		<u>(% W/W)</u>				
<u>Ingredient</u>		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>
5	<u>PART A</u>					
	Stearic Acid	5.00	5.00	5.00	5.00	5.00
	Parsol MCX (Octyl-methoxycinnamate)	7.50	7.50	7.50	7.50	7.50
10	Escalol 567 (Benzophenone-3)	3.00	3.0	3.00	3.00	3.00
	Mineral Oil	10.00	-	-	-	-
	PEG-7 glyceryl cocoate	-	5.00	5.00	7.50	-
	Pentaerythrityl tetrapelargonate	-	5.00	-	-	7.50
15	Propylene glycol isostearate	-	-	5.00	-	-
	Polyglycerol-3 diisostearate	-	-	-	2.50	2.50
	<u>PART B</u>					
20	Water	51.80	51.80	51.80	51.80	51.80
	2% Carbopol 941	20.00	20.00	20.00	20.00	20.00
	Triethanolamine	2.45	2.45	2.45	2.45	2.45
	<u>PART C</u>					
25	Glydant (antioxidant)	0.25	0.25	0.25	0.25	0.25
	TOTAL	100.00	100.00	100.00	100.00	100.00

Example 1 (cont.)

		<u>(% W/W)</u>			
<u>Ingredient</u>		<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>
<u>PART A</u>					
5	Stearic Acid	5.00	5.00	5.00	5.00
	Parsol MCX (Octyl-methoxycinnamate)	7.50	7.50	7.50	7.50
	Escalol 567 (Benzophenone-3)	3.00	3.00	3.00	3.00
10	PPG-5-laureth-5	5.00	2.50	-	
	Caprylic/Capric triglyceride	5.00	5.00	2.50	2.50
	PPG-2-ceteareth-9	-	5.00	-	2.50
	Polysorbate 80	-	-	5.00	-
15	Polysorbate 20	-	-	-	5.00
<u>PART B</u>					
	Water	51.80	51.80	51.80	51.80
	2% Carbopol 941	20.00	20.00	20.00	20.00
	Triethanolamine	2.45	2.45	2.45	2.45
20	<u>PART C</u>				
	Glydant (antioxidant)	0.25	0.25	0.25	0.25
	TOTAL	100.00	100.00	100.00	100.00

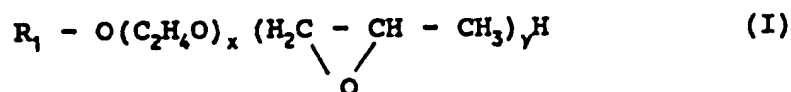
Example 2

The SPF values of various emulsions which contain benzophenone-3 and octyl methoxycinnamate were as follows:

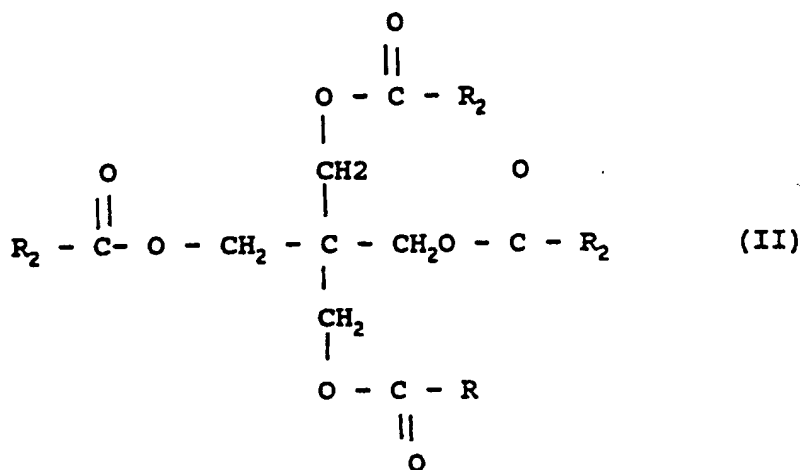
	<u>Formulation</u>	<u>Emollient System</u>	<u>SPF Value</u>
5	1	Mineral Oil (as a control)	10.7
	2	PEG-7 glyceryl cocoate: pentaerythrityl tetrapelargonate (50:50)	13.2
10	3	PEG-7 glyceryl cocoate: propylene glycol isostearate (50:50)	13.2
	4	PEG-7 glyceryl cocoate: polyglycerol-3 diisostearate (75:25)	13.2
15	5	pentaerythrityl tetrapelargonate: polyglycerol-3 diisostearate (75:25)	11.6
	6	PPG-5-laureth-5: caprylic/capric triglyceride (50:50)	13.5
	7	PPG-2-ceteareth-9: caprylic/capric triglyceride (50:50)	16.5
20	8	Polysorbate 20 : PPG-5-laureth-5: caprylic/capric triglyceride (50:25:25)	13.8
	9	Polysorbate 80 : PPG-2-ceteareth-9; caprylic/capric triglyceride (50:25:25)	10.5

WHAT IS CLAIMED IS:

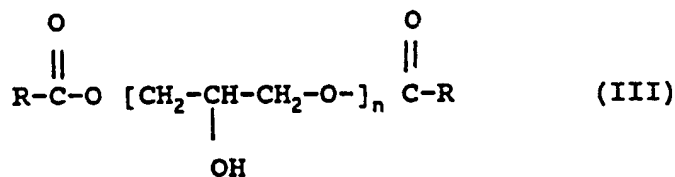
1. A method for increasing the UV absorbance of octyl methoxycinnamate which comprises dissolving an effective amount in an emollient system comprising compounds of the formula or mixtures thereof:



wherein R_1 is C_{10} - C_{18} straight or branched chain alkyl, x is an integer of 5 to 10 and y is an integer of 2 to 6.

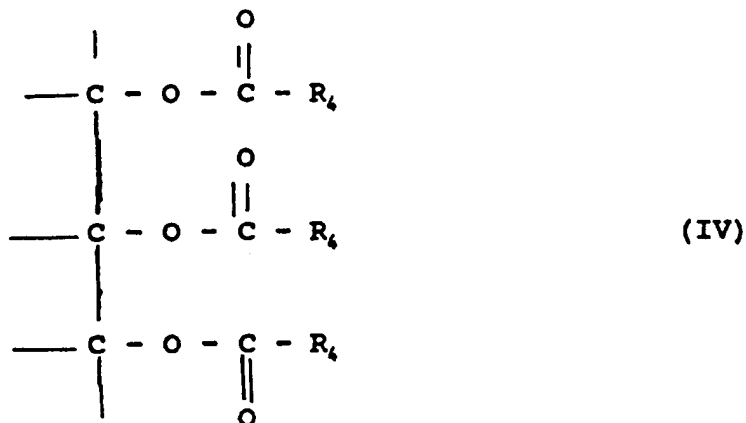


wherein $R_2\text{CO}$ is a pelargonic acid radical

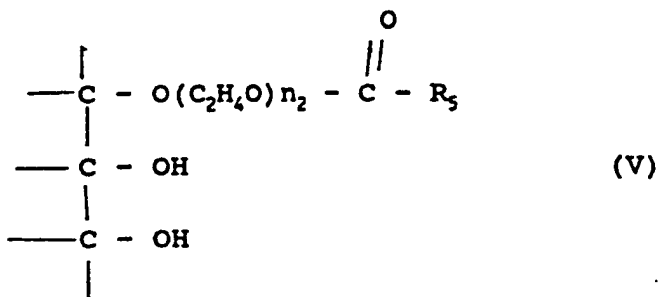


wherein R is an isostearic acid radical and n is an integer of 2 to 5.

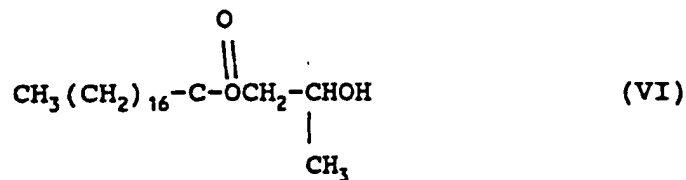
5



10 wherein R₄ is C₈ to C₁₂ alkyl, and



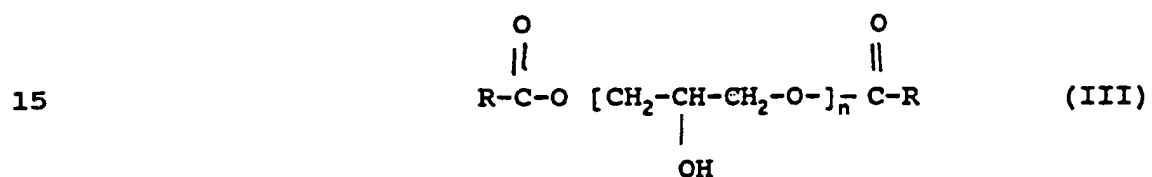
15 wherein R₅CO=COCO and n₂ is an integer of 4 to 9, and



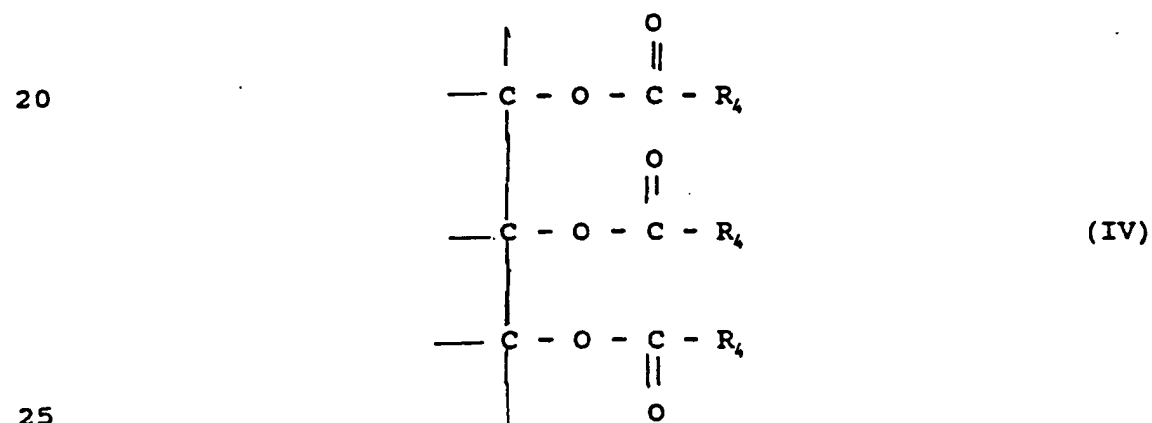
2. A method according to claim 1 wherein the emollient system comprises a mixture of PEG-7 glyceryl cocoate : pentaerythrityl tetrapelargonate a ratio of about 75:25.

20

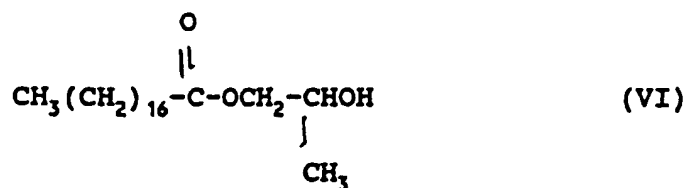
3. A method according to claim 1 wherein the emollient system comprises PPG-2-ceteareth-9 : caprylic/capric triglyceride at a ratio of 50:50.
4. A method according to claim 1 wherein the emollient system comprises polysorbate 20 : PPG-2-ceteareth-9 : caprylic/capric triglyceride at a ratio of about 50:25:25.
5. A method according to claim 1 wherein the emollient system comprises PEG-7-glyceryl cocoate: propylene glycol isostearate at a ratio of 50:50.
6. A method for increasing the UV absorbance of benzophenone-3 which comprises dissolving an effective amount of benzophenone-3 in an emollient system comprising compounds III, IV or VI alone or mixtures thereof.



wherein R is an isostearic acid radical and n is an integer of 2 to 5.



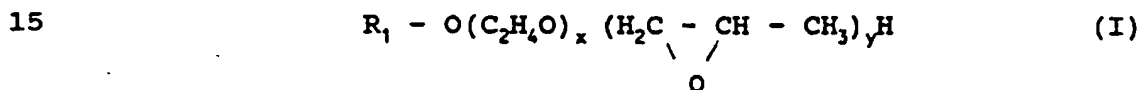
wherein R_1 is C_8 to C_{12} alkyl, and



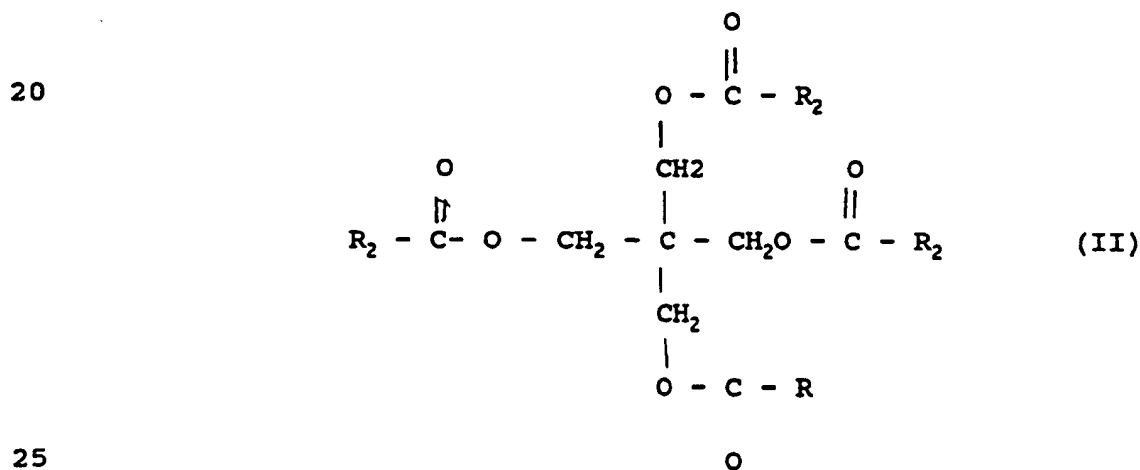
5 7. A method according to claim 6 wherein the emollient system comprises PEG-7 glyceryl cocoate : polyglycerol-3 diisostearate at a ratio of 75:25.

8. A method according to claim 6 wherein the emollient system comprises polysorbate 80 : PPG-5-laureth-5 :
10 caprylic/capric triglyceride at a ratio of 50:25:25.

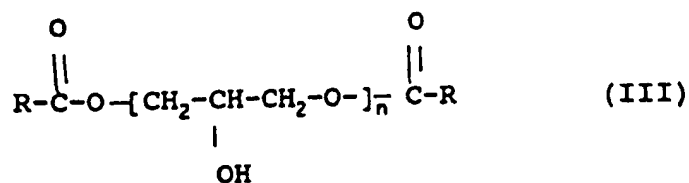
9. A composition having an increased UV absorbance of octyl methoxycinnamate which comprises an effective amount of said octyl methoxycinnamate in an emollient system comprising compounds of the formula or mixtures thereof:



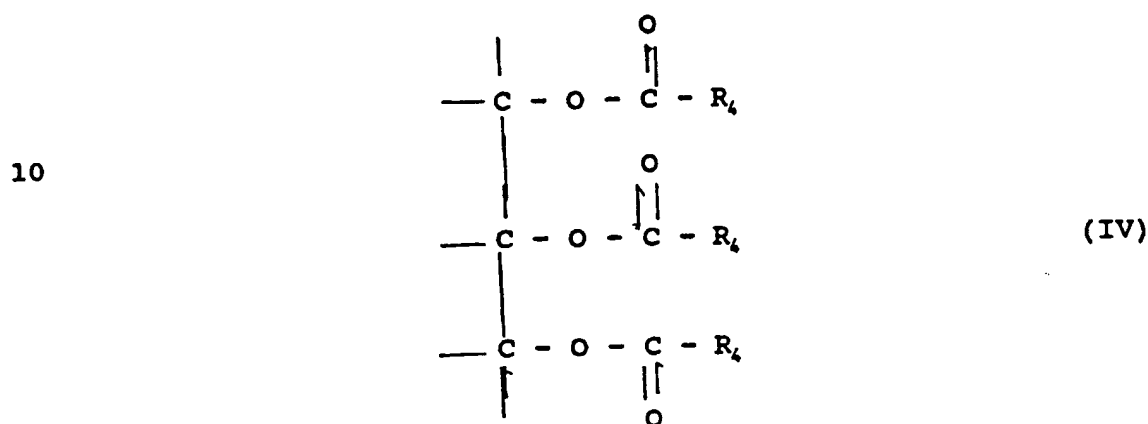
wherein R_1 is C_{10} - C_{18} straight or branched chain alkyl, x is an integer of 5 to 10 and y is an integer of 2 to 6.



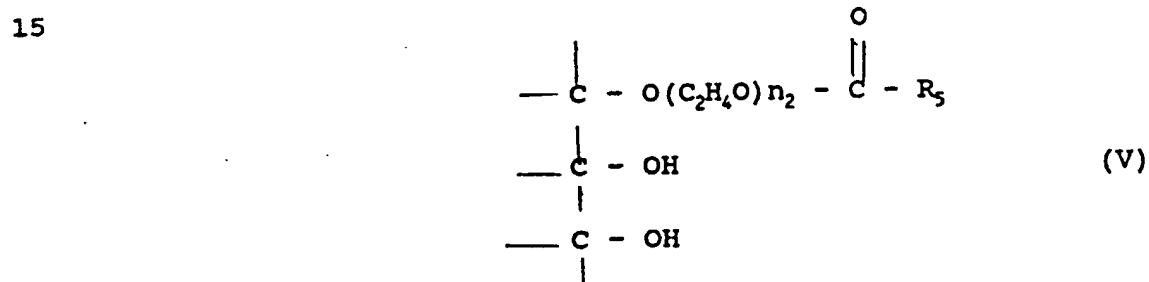
wherein R_2CO is a pelargonic acid radical



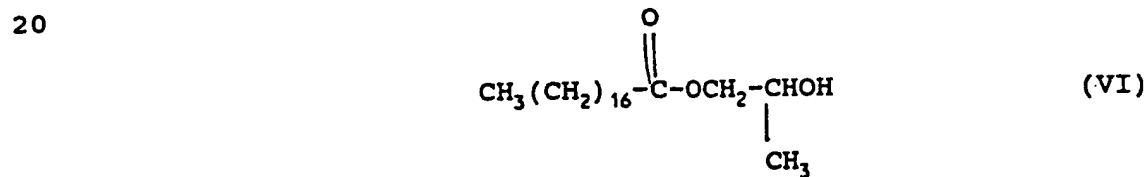
5 wherein R is an isostearic acid radical and n is an integer of 2 to 5.



wherein R_4 is C_8 to C_{12} alkyl, and



wherein $R_5CO=COCO$ and n_2 is an integer of 4 to 9.

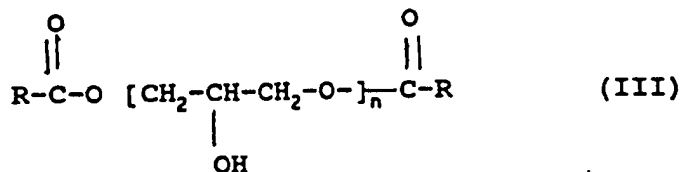


10. A composition according to claim 9 wherein the emollient system comprises a mixture of PEG-7 glyceryl cocoate : pentaerythritol tetrapelargonate a ratio of about 75:25.

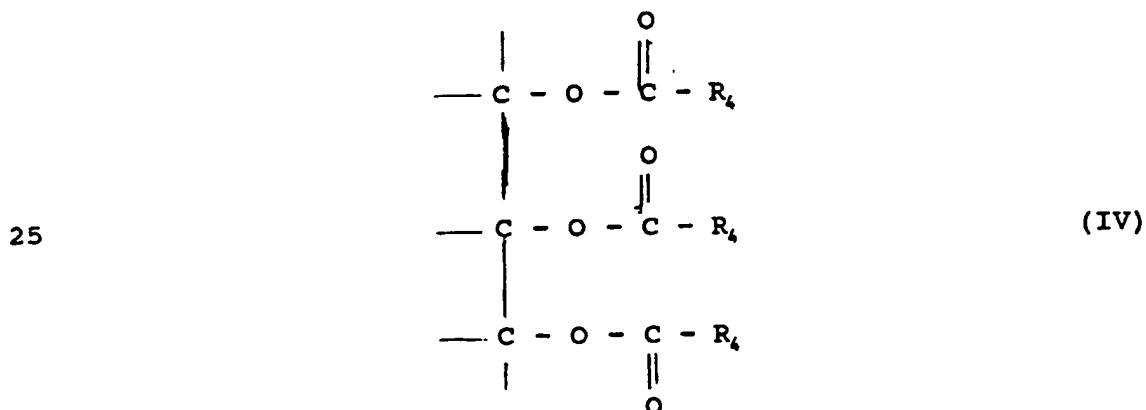
5 11. A composition according to claim 9 wherein the emollient system comprises PPG-2-cetareth-9 : caprylic/capric triglyceride at a ratio of 50:50.

12. A composition according to claim 1 wherein the emollient system comprises polysorbate 20 : PPG-2-cetareth-9 : caprylic/capric triglyceride at a ratio of about 50:25:25.

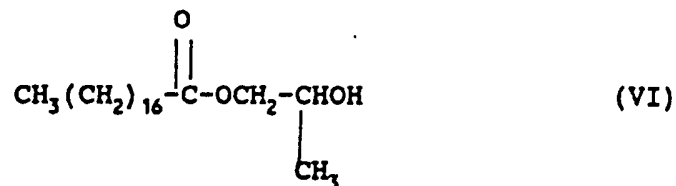
13. A composition having an increased UV absorbance of benzophenone-3 which comprises an effective amount of said benzophenone-3 in an emollient system comprising compounds
15 III, IV or VI alone or mixtures thereof.



20 wherein R is an isostearic acid radical and n is an integer of 2 to 5.



wherein R_4 is C_8 to C_{12} alkyl, and



- 5 14. A composition according to claim 12 wherein the emollient system comprises PEG-7 glyceryl cocoate : polyglycerol-3 diisostearate at a ratio of 75:25.
- 10 15. A composition according to claim 12 wherein the emollient system comprises polysorbate 80 : PPG-5-laureth-5 : caprylic/capric triglyceride at a ratio of 50:25:25.

INTERNATIONAL SEARCH REPORT

PCT/US 92/08215

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 A61K7/42; A61K7/48		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with Indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	FR,A,2 340 086 (BAYER) 2 September 1977 see page 1, line 20 - line 27 see page 2, line 27 - page 3, line 15; examples 4,7-9 ---	1,9
X	EP,A,0 418 443 (NEUTROGENA CORPORATION) 27 March 1991 cited in the application see page 5, line 25 - line 32; examples 2,8 & US,A,4 894 222 ---	9
X	US,A,4 264 581 (KERKHOF ET AL.) 28 April 1981 see the whole document ---	13
-/--		
<p>¹⁰ Special categories of cited documents : ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
03 MAY 1993	79. 06. 26	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	FISCHER J.P.	

INTERNATIONAL SEARCH REPORT

PCT/US 92/08215

International Application No

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		Relevant to Claim No.
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	
X	EP,A,0 165 457 (HENKEL) 27 December 1985 see example 2.5 ---	9
X	FR,A,2 670 111 (BOSSERELLE) 12 June 1992 see the whole document ---	9,13
A	US,A,4 384 974 (GUTHAUSER) 24 May 1983 see the whole document ---	9,13
A	US,A,4 940 574 (KAPLAN) 10 July 1990 cited in the application see column 3, line 64 - column 4, line 15; claim 1 & US,A,4 940 574 ---	9
A	S.T.N., FILE SUPPLIER, KARLSRUHE, DE File Chemical Abstracts, vol 111, an : 219316 see the abstract & JP,A,1 143 831 (NISSAN CHEMICAL INDUSTRIES) -----	1

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9208215
SA 65656

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 03/05/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A-2340086	02-09-77	DE-A- 2604121	11-08-77
		BE-A- 851087	04-08-77
		CH-A- 625957	30-10-81
		GB-A- 1555204	07-11-79
		NL-A- 7701106	08-08-77
		SE-B- 440447	05-08-85
		SE-A- 7701174	05-08-77

EP-A-0418443	27-03-91	US-A- 4894222	16-01-90
		AU-B- 625368	09-07-92
		AU-A- 4152189	20-06-91

US-A-4264581	28-04-81	None	

EP-A-0165457	27-12-85	DE-A- 3418887	21-11-85
		JP-A- 60260508	23-12-85

FR-A-2670111	12-06-92	AU-A- 8960691	18-06-92

US-A-4384974	24-05-83	None	

US-A-4940574	10-07-90	CA-A- 2006168	22-06-90
